(FILE 'HOME' ENTERED AT 18:48:08 ON 09 FEB 2002)

FILE 'USPATFULL' ENTERED AT 18:48:30 ON 09 FEB 2002

L1 3949 SEA URIDINE
L2 0 SEA L1 AND ELEVATED PURINE LEVEL
L3 0 SEA L1 AND PERVASIVE(W)DEVELOPMENTAL(W)DISORDER
L4 11 SEA L1 AND AUTISM
D L4 1-11, TI, KWIC
D L4 7 STD, AB, KWIC

FILE 'CAPLUS' ENTERED AT 18:55:45 ON 09 FEB 2002

L5 23277 SEA URIDINE
L6 6 SEA L5 AND ATAXIA
D L6 1-6
D L6 1-2 STD, AB, KWIC

L4 ANSWER 7 OF 11 USPATFULL
AN 2001:139534 USPATFULL
TI Compositions and methods for treatment of mitochondrial diseases
IN von Borstel, Reid W., Potomac, MD, United States
PA Pro-Neuron, Inc. (U.S. corporation)
PI US 2001016576 A1 20010823
AI US 2001-838136 A1 20010420 (9)
RLI Continuation of Ser. No. US 1998-144096, filed on 31 Aug 1998, PENDING
DT Utility
FS APPLICATION
LN.CNT 1390
INCL INCLM: 514/044.000
NCL NCLM: 514/044.000
IC [7]
ICM: A61K048-00
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compounds, compositions, and methods are provided for treatment of disorders related to mitochondrial dysfunction. The methods comprise administering to a mammal a composition containing pyrimidine nucleotide precursors in amounts sufficient to treat symptoms resulting from mitochondrial respiratory chain deficiencies.
SUMM [0008] Commonly owned U.S. Pat. No. 5,583,117 discloses acylated derivatives of cytidine and **uridine**. Commonly owned application PCT/US 96/10067 discloses the use of acylated pyrimidine nucleosides to reduce the toxicity of chemotherapeutic and antiviral. . .
DETD [0038] Dihydro-orotate dehydrogenase (DHODH), is an enzyme involved in de novo synthesis of **uridine** nucleotides. DHODH activity is coupled to the respiratory chain via transfer of electrons from dihydro-orotate to ubiquinone; these electrons are. . . Complexes III and IV are directly involved in pyrimidine biosynthesis. Orotate produced by the action of DHODH is converted to **uridine** monophosphate by phosphoribosylation and decarboxylation.
DETD . . . either distal to DHODH (e.g. orotate) or which do not require DHODH activity for conversion to pyrimidine nucleotides (e.g. cytidine, **uridine**, or acyl derivatives of cytidine or **uridine**). Also included within the scope of the invention are pyrimidine nucleoside phosphates (e.g. nucleotides, cytidine diphosphocholine, **uridine** diphosphoglucose); these compounds are degraded to the level of **uridine** or cytidine prior to entry into cells and anabolism. Acyl derivatives of cytidine and **uridine** have better oral bioavailability than the parent nucleosides or nucleotides. Orotic acid and esters thereof are converted to **uridine** nucleotides and are also useful for accomplishing the goals of the invention.
DETD [0042] Tissue pyrimidine nucleotide levels are increased by administration of any of several precursors. **Uridine** and cytidine are incorporated into cellular nucleotide pools by phosphorylation at the 5' position; cytidine and **uridine** nucleotides are interconvertible through enzymatic amination and de-amination reactions. Orotic acid is a key intermediate in de novo biosynthesis of. . . into nucleotide pools requires cellular phosphoribosyl pyrophosphate (PRPP). Alternatively (or in addition to provision of exogenous nucleotide precursors), availability of **uridine** to tissues is increased by administration of compounds which inhibit **uridine** phosphorylase, the first enzyme in the pathway for degradation of **uridine**. The compounds of the invention useful in treating mitochondrial diseases and related disorders include **uridine**, cytidine, orotate, orally bioavailable acyl derivatives or esters of these pyrimidine nucleotide precursors, and inhibitors of the enzyme **uridine** phosphorylase.

DETD [0043] In reference to acyl derivatives of cytidine and **uridine**, the following definitions pertain:

DETD [0051] (1) An acyl derivative of **uridine** having the formula: ##STR1##

DETD [0056] (3) An acyl derivative of **uridine** having the formula: ##STR3##

DETD [0068] (5) An acyl derivative of **uridine** having the formula: ##STR5##

DETD [0077] Advantageous compounds of the invention are short-chain (2 to 6 carbon atoms) fatty acid esters of **uridine** or cytidine. Particularly advantageous compounds are triacetyluridine or triacetylcytidine. Such compounds have better oral bioavailabilty than the parent nucleosides, and. . .

DETD [0079] **Uridine** tripyruvate (2',3',5'-tri-O-pyruvyluridine) provides the benefits of both pyrimidines and pyruvate, delivering both with a single chemical entity, and avoiding the. . .

DETD [0080] Inhibitors of **uridine** phosphorylase

DETD [0081] An alternative or complementary strategy for treating mitochondrial diseases involves inhibition of **uridine** catabolism with an inhibitor of the enzyme **uridine** phosphorylase.

DETD [0082] Examples of inhibitors of **uridine** phosphorylase that are useful for treatment of mitochondrial disease include but are not limited to 5-benzyl barbiturate or 5-benzylidene barbiturate. . .

DETD . . . novel pharmaceutical compositions comprise as an active agent one or more pyrimidine nucleotide precursors selected from the group consisting of **uridine**, cytidine, orotic acid or its salts or esters, and acyl derivatives of these pyrimidine nucleotide precursors, together with a pharmaceutically. . .

DETD . . . of the invention, the composition comprises at least one pyrimidine nucleotide precursor and an agent which inhibits the degradation of **uridine**, such as an inhibitor of the enzyme **uridine** phosphorylase. Examples of inhibitors of **uridine** phosphorylase include but are not limited to 5-benzyl barbiturate or 5-benzylidene barbiturate derivatives including 5-benzyl barbiturate, 5-benzyloxybenzyl barbiturate, 5-benzyloxybenzyl- 1-[(1-hydroxy-2-ethoxy)methyl]. . . -acyclouridine, aminomethyl-benzylacyclouridine, aminomethylbenzyloxybenzylacyclouridine, hydroxymethyl-benzylacyclouridine, and hydroxymethyl-benzyloxybenzylacyclouridine. Furthermore, it is within the scope of the invention to utilize an inhibitor of **uridine** phosphorylase alone, without coadministration of a pyrimidine nucleotide precursor, for the purpose of treating mitochondrial diseases or pathophysiologies associated with. . .

DETD . . . as diminished ATP synthesis via oxidative phosphorylation. Human cells proliferate and retain viability under virtually anaerobic conditions if provided with **uridine** and pyruvate (or a similarly effective agent for oxidizing NADH to optimize glycolytic ATP production). Nuclear-mitochondrial interactions: Transcription of mitochondrial. . .

DETD . . . shutdown of respiratory chain activity) can survive in culture if provided with two agents which compensate for critical rnitochondrial functions: **uridine** and pyruvate. **Uridine** is required in vitro because a limiting enzyme for +E,uns de novosynthesis of **uridine** nucleotides, dihydro-orotate dehydrogenase (DHODH), is coupled to the mitochondrial respiratory chain, via ubiquinone as a proximal electron acceptor, cytochrome c. . . Mol. Cell. Biochem. 174:125-129, 1997). DHODH is required for synthesis of orotate, which is then phosphoribosylated and decarboxylated to produce **uridine** monophosphate (UMP). All other pyrimidines in cells are derived from UMP. Cells from patients with mitochondrial disease due to defects in mitochondrial DNA require exogenous **uridine** in order to

survive outside of the milieu of the body, wherein pyrimidines, derived from other cells or the diet,. . .

DETD . . . requires intensive biosynthetic activity, particularly involving synthesis of neuronal membranes and myelin, both of which require pyrimidine nucleotides as cofactors. **Uridine** nucleotides are involved in activation and transfer of sugars to glycolipids and glycoproteins. Cytidine nucleotides are derived from **uridine** nucleotides, and are crucial for synthesis of major membrane phospholipid constituents like phosphatidylcholine, which receives its choline moiety from cytidine. . . circuits, resulting in delayed or arrested development of neuropsychological functions like language, motor, social, executive function, and cognitive skills. In **autism** for example, magnetic resonance spectroscopy measurements of cerebral phosphate compounds indicates that there is global undersynthesis of membranes and membrane precursors indicated by reduced levels of **uridine** diphospho-sugars, and cytidine nucleotide derivatives involved in membrane synthesis (Minshew et al., Biological Psychiatry 33:762-773, 1993).

DETD . . . Syndrome, pervasive developmental delay (or PDD-NOS: "pervasive developmental delay - not otherwise specified" to distinguish it from specific subcategories like **autism**), **autism**, Asperger's Syndrome, and Attention Deficit/Hyperactivity Disorder (ADHD), which is becoming recognized as a delay or lag in development of neural. . .

DETD . . . therapy of mitochondriai disease, compounds of the invention are typically administered one to three times per day. Acyl derivatives of **uridine** and cytidine are administered orally in doses of 0.01 to 0.5 grams per kilogram of body weight per day, with. . .

DETD [0169] In the case of patients unable to receive oral medications, compounds of the invention, especially **uridine**, cytidine, and orotate esters can be administered, as required, by prolonged intravenous infusion, delivering daily doses of 0.01 to 0.5. . .

DETD [0180] Acyl derivatives of cytidine and **uridine** are synthesized typically by acylation methods involving reaction of acid chlorides or acid anhydrides with cytidine or **uridine**.

DETD [0200] Example 6: Synthesis of **Uridine** Pyruvate A. The preparation of pyruvyl chloride was accomplished by the reaction of alpha, alpha-dichloromethyl methyl ether and pyruvic acid using the procedure of Ottenheum and Man (Synthesis, 1975, p. 163). B. **Uridine** (3.0 g, 12 nmol) was dried by toluene azeotrope under vacuum (3x), and then dissolved in DMF (20 mL) and. . . mixture was stirred at room temperature under argon for 24 hours. Analysis by TLC (5% MeOH/CH.sub.2Cl.sub.2) showed the consumption of **uridine**. The reaction mixture was evaporated to dryness and partitioned between CH.sub.2Cl.sub.2 and aqueous sodium bicarbonate. The organic layer was washed. . . water; dried over sodium sulfate; concentrated; and purified using flash chromatography (silica gel, 5% MeOH/CH.sub.2Cl.sub.2) to yield 1.4 g of **uridine** pyruvate, or 2',3',5'-tri-0-pyruvyluridine.

CLM What is claimed is:

11. A method as in claim 1 wherein said pyrimidine nucleotide precursor is selected from the group consisting of **uridine**, cytidine, an acyl derivative of **uridine**, an acyl derivative of cytidine, orotic acid, an alcohol ester of orotic acid, or a pharmaceutically acceptable salt thereof.

13. A method as in claim 11 wherein said pyrimidine nucleotide precursor is an acyl derivative of **uridine**.

14. A method as in claim 11 wherein said acyl derivative of **uridine** is 2',3',5'-tri-O-acetyluridine.

15. A method as in claim 11 wherein said acyl derivative of **uridine** is 2',3',5'-tri-O-pyruvyluridine.

40. A method as in claim 36 wherein said developmental delay is **autism**.

6 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2002 ACS
AN 2000:161074 CAPLUS
DN 132:203149
TI Compositions and methods using pyrimidine nucleotide precursors for treatment of mitochondrial diseases
IN Von Borstel, Reid W.
PA Pro-Neuron, Inc., USA
SO PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000011952	A1	20000309	WO 1999-US19725	19990831
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 2001005719	A1	20010628	US 1998-144096	19980831
	AU 9960219	A1	20000321	AU 1999-60219	19990831
	BR 9913319	A	20010522	BR 1999-13319	19990831
	EP 1109453	A1	20010627	EP 1999-968207	19990831
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	US 2001016576	A1	20010823	US 2001-838136	20010420
PRAI	US 1998-144096	A2	19980831		
	WO 1999-US19725	W	19990831		

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2002 ACS
AN 2000:98343 CAPLUS
DN 132:132349
TI Methods using **uridine** or a **uridine** source for increasing cytidine levels in vivo and treating cytidine-dependent human neurological diseases
IN Watkins, Carol; Wurtman, Richard J.
PA Massachusetts Institute of Technology, USA
SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000006174	A1	20000210	WO 1999-US17235	19990730
	W: CA, JP				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	EP 1140104	A1	20011010	EP 1999-937631	19990730
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRAI	US 1998-95002	P	19980731		
	WO 1999-US17235	W	19990730		

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2002 ACS
AN 2000:161074 CAPLUS
DN 132:203149
TI Compositions and methods using pyrimidine nucleotide precursors for treatment of mitochondrial diseases
IN Von Borstel, Reid W.
PA Pro-Neuron, Inc., USA
SO PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A01N043-04
ICS A61K031-70
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000011952	A1	20000309	WO 1999-US19725	19990831
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 2001005719	A1	20010628	US 1998-144096	19980831
	AU 9960219	A1	20000321	AU 1999-60219	19990831
	BR 9913319	A	20010522	BR 1999-13319	19990831
	EP 1109453	A1	20010627	EP 1999-968207	19990831
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	US 2001016576	A1	20010823	US 2001-838136	20010420
PRAI	US 1998-144096	A2	19980831		
	WO 1999-US19725	W	19990831		

AB Compds., compns., and methods are provided for treatment of disorders related to mitochondrial dysfunction. The methods comprise administering to a mammal a compn. contg. pyrimidine nucleotide precursors in amts. sufficient to treat symptoms resulting from mitochondrial respiratory chain deficiencies.

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT Nervous system
(Friedreich's **ataxia**; pyrimidine nucleotide precursors for treatment of mitochondrial diseases)

IT Disease, animal
(NARP (neurogenic muscle weakness, **ataxia**, and retinitis pigmentosa); pyrimidine nucleotide precursors for treatment of mitochondrial diseases)

IT Nervous system
(**ataxia**; pyrimidine nucleotide precursors for treatment of mitochondrial diseases)

IT 58-96-8, **Uridine**
RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pyrimidine nucleotide precursors for treatment of mitochondrial diseases)

IT 58-96-8D, **Uridine**, acyl derivs. 65-46-3, Cytidine 65-46-3D, Cytidine, acyl derivs. 65-86-1, Orotic acid 65-86-1D, Orotic acid, esters 127-17-3, Pyruvic acid, biological studies 127-17-3D, Pyruvic acid, esters 987-78-0, Cytidine diphosphocholine 1747-53-1, Ethyl